Vascular markers and endovascular therapy in peripheral arterial disease

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Vascular Markers and Endovascular Therapy in Peripheral Arterial Disease

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Introduction

Biomarkers are used to examine normal biological processes, pathogenic processes, or responses to a therapeutic intervention. In vascular disease, widely accepted biomarkers are high sensitive C-reactive protein or markers of lipid metabolism such as low cholesterol lipoprotein. Functional vascular markers are blood pressure, ratios of upper and lower limbs blood pressures, the ankle-brachial pressure index (ABI), or aortic augmentation index and flow-mediate dilation. Such markers are helpful for stratification of a vascular disease. For example, the ABI allows the assessment of the severity of peripheral arterial disease. In addition, vascular markers are surrogate indicators for adverse events and prognosis. Hence, it is of great interest and importance to study the impact of therapeutic interventions on these markers.

Diagnosis and therapy in medicine are challenged to give optimal information and treatment ideally based on a non-invasive or minimally invasive procedure. Focus of my research is to investigate the impact of percutaneous transluminal angioplasty (PTA) on vascular markers in peripheral and renal atherosclerotic disease and to expand the endovascular treatment options as a minimally invasive alternative to open vascular surgery.

Markers for vascular function in peripheral arterial and renovascular disease [1-3]

A simple vascular biomarkers such as the ankle-brachial index, which is basically the ratio of brachial and ankle systolic blood pressure, is a cheap and reliable test for the assessment of lower limb perfusion and an independent predictor for cardiovascular morbidity. In addition, it is used to assess changes in lower limb perfusion following arterial revascularization. Although it is an indicator of generalized atherosclerosis, the cause for its powerful prediction of mortality in relation to the amount of lower limb perfusion impairment is less clear. In recent years, arterial stiffness and central aortic pressure augmentation have received great interest in vascular research and are, as the ABI, independent predictors for mortality. PAD is characterized by extensive atherosclerotic changes along the vascular tree as well as inflammatory processes and elevated central aortic pressures.

We investigate whether ABI impairment correlates with aortic pressure augmentation (AIx) and subendocardial viability ratio (SEVR), a measure of cardiac perfusion during diastole. By using radial applanation tonometry in patients with stable PAD (Rutherford stage I-III) we found that AIx was significantly negatively associated with ABI (β=-11.5; 95% confidence interval [CI], -18.6 to -4.5; P=.002). In addition to other factors that are known to be associated with AIx such as diastolic blood pressure, height and smoking. Moreover, SEVR as a dependent variable showed a significant correlation with ABI (β=33.2; 95% CI, 2.3-64.1; P=.036).

Subsequently, we were able to demonstrate that endovascular lower-limb revascularization does not only improve ABI, but was associated lower central aortic pressure index. In a controlled non-randomized trial, ABI and AIx of patients with PAD undergoing lower limb revascularization for intermittent claudication were compared to conservatively treated PAD patients with claudication. During a three months follow-up, AIx significantly lowered by 10% compared to baseline values, whereas AIx in the control group remained unchanged.

We therefore concluded that severity of lower limb perfusion impairment is related to central aortic pressure augmentation and to subendocardial viability ratio in PAD patients. This might be a potential pathophysiologic link that impacts cardiac prognosis in patients with PAD. Since vascular markers such as ABI and AIx are surrogate indicator for prognosis, our results call for larger randomized trials to determine the role of lower limb revascularization on cardiovascular outcome in patients with PAD and claudication.

Similarly to PAD, renovascular disease may cause arterial hypertension and impair endothelial function which is like ABI and AIx a marker for cardiovascular risk. In a study, endothelial function was assessed by high-resolution ultrasound as flow mediated dilatation of the brachial artery in patients with renovascular disease undergoing renal artery interventions. Endothelial-dependent dilatation improved from 2.4±0.9% to 6.1±1.4% ($P=0.03$), whereas endothelial-independent dilatation remained unchanged following renal intervention. Furthermore, endothelial-dependent reactive hyperemic blood flow increased from 195±40 mL/min to 536±94 mL/min ($P=0.0008$) and remained unaffected during endothelial-independent hyperemia. We also found that shear stress at rest decreased from 37±11 to 23±3 dyne/cm² ($P<0.0001$), and reactive hyperemic shear stress increased from 89±29 to 107±12 dyne/cm² ($P=0.014$).

Although our study results were in agreement with previous important studies on endothelial function in renovascular disease, the recent clinical endpoint studies ASTRAL and CORAL did not confirm that renal angioplasty impact morbidity or mortality when compared to conservative treatment in patients with renovascular disease.

Taken together our insight from functional vascular markers in PAD and renovascular disease, it seems that vascular function is impaired in the presence of atherosclerotic disease and improves upon revascularization procedures, but it remains at least for PAD unclear whether this will result in improved survival, whereas in view of the latest clinical trials on renovascular disease is now highly questioned. Nevertheless, our and others' observation of vascular function a least shed an insight on pathophysiological mechanisms and that revascularization impact systemic vascular function.

Small dense low density lipoprotein particles are associated with poor outcome after angioplasty in peripheral artery disease [4]

In recent years, it became evident that not only the amount of low density lipoprotein (LDL) is associated with adverse cardiovascular outcome, but that also size of LDL is of importance. The presence of small dense LDL is an established cardiovascular risk factor and associated with cardiovascular events and progression of coronary artery disease. However, the role of small dense LDL in the process of restenosis following an angioplasty in peripheral arterial disease is unknown.

In a prospective, observational study, elevated plasma levels of small dense LDL particles were associated with worse early outcome in patients undergoing percutaneous revascularization for symptomatic PAD (n=60). Patients with improved walking distance and without restenosis after revascularization had a significant larger LDL size at baseline (26.6±1.1nm vs. 26.1±1.1nm, $p<0.05$) and at follow-up (26.7±1.1nm vs. 26.2±0.9nm, $p<0.05$) than patients without improvement.

The results need confirmation in a larger study since size of LDL level may be associated with outcome following angioplasty and therefore optimize patient selection for adequate treatment.

Stent-assisted angioplasty at the level of the common femoral artery bifurcation [5]

Since the introduction of the principle of balloon angioplasty by Andreas Grüntzig 40 years ago at the University Hospital of Zurich, there has been an enormous development in endovascular therapy especially in terms of improvement of patency following the introduction of stents. Angioplasty is now first-choice therapy for most iliac and infrainguinal atherosclerotic lesions offering the advantage of a percutaneous and minimally invasive approach in local anesthesia for the usually frail PAD patients. Although vascular surgery is reserved for cases which are not amendable for angioplasty, the common femoral region persisted to be a domain of vascular surgery. To overcome this limitation of angioplasty for the common femoral bifurcation, we were one of the first to show that stent-implantation in the common femoral artery is feasible with 100% success rate and cumulative primary patency of 83% at three years.

This has clinical implication for the increasing elderly and frail population with PAD and critical limb ischemia. In most cases, there is multilevel arterial obstruction, most of which are usually treated by angioplasty. Hence, in cases with obstruction at the femoral bifurcation, angioplasty with stenting is an alternative treatment to surgery at least in multimorbid patients with multilevel disease.

Conclusion

Assessment and exploration of biomarkers of vascular function and disease are important for pathophysiologic insights and may detected subclinical changes. Functional or humoral markers for vascular disease need further evaluation in different clinical settings. In view of a growing elderly population with vascular disease, reliable markers for the disease as well as minimally invasive procedures continue to be warranted.

References

1. Mosimann K, Jacomella V, Thalhammer C, Meier TO, Kohler M, Amann-Vesti B*, et al.* Severity of peripheral arterial disease is associated with aortic pressure augmentation and subendocardial viability ratio. *J Clin Hypertens (Greenwich)* 2012,**14**:855-860.

2. Jacomella V, Shenoy A, Mosimann K, Kohler MK, Amann-Vesti B, Husmann M. The impact of endovascular lower-limb revascularisation on the aortic augmentation index in patients with peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2013,**45**:497-501.

3. Jacomella V, Husmann M, Thalhammer C, Uike K, Pfammatter T, Amann-Vesti B. Impact of endovascular treatment of atherosclerotic renal artery stenosis on endothelial function and arterial blood pressure. *Int Angiol* 2012,**31**:70-76.

4. Jacomella V, Gerber PA, Mosimann K, Husmann M, Thalhammer C, Wilkinson I*, et al.* Small dense low density lipoprotein particles are associated with poor outcome after angioplasty in peripheral artery disease. *PLoS One* 2014,**9**:e108813.

5. Stricker H, Jacomella V. Stent-assisted angioplasty at the level of the common femoral artery bifurcation: midterm outcomes. *J Endovasc Ther* 2004,**11**:281-286.